Monsanto

FROM (NAME & LOCATION) Dept. of Medicine & Environmental Health

DATE: December 17, 1975 CC:

SUBJECT: EPA PROPOSED STANDARD FOR VINYL CHLORIDE PLANT EMISSIONS

REFERENCE:

TO Mr. J. W. Hanley

Mr. Train announced yesterday EPA was proposing a standard which would limit the release of vinyl chloride from plants in which vinyl chloride is handled to concentrations below 0.1 ppm. The proposal will be published in the Federal Register after which there will be a 45 day period for public comment and a public hearing.

The proposed standard will have little to no impact on Monsanto. Comments in the Wall Street Journal story enclosed indicate that major producers will be able to comply.

Of more concern is the reasoning that has led to the standard proposal and the precedents it may be setting for future EPA action. EPA reasons that -

1. Vinyl chloride is a carcinogen
2. It has been detected in air of neighborhoods surrounding plants where it is made or used
3. The claim is made that angiosarcoma cases have been found among populations around these plants - (not really established).

Therefore, it must be regulated, and since costs to industry are slight they are proceeding.

We are concerned that similar reasoning could also be applied to any of the 1500 suspected carcinogens. Consequences of such action would be very significant.

George Roush, Jr., M. D.

GR/ln
enc.

RSV 0011102

IN-1DM 12/75

To File: (PENNWALT + MIASA)

Subject: VCM - Liver Cancer

John Fox called 4/10/74 to say latest Federal Register reports OSHA is proposing zero ppm VCM

apparently based on a 7-month tests run for the NCA in which 2 of 200 mice got angio-sarcoma when exposed to 50 ppm VCM for 7 hrs/day.

Buck Cooper has a GLPC analytical method (modified Dow method) - he will send me a copy.

John Fox will send a Xerox of the above-mentioned article in the Federal Register.

HTM

RSV 0011104

SUGGESTED DISCUSSION OUTLINE
FOR USE WITH EMPLOYEES FROM OLD VCM PLANT

You must have seen the recent publications in regard to some cases of liver cancer which have occurred in a Goodrich polyvinyl chloride plant. At this time there is a known total of six cases of such illness. This is a total of six at some 37 plants, with a total of 6500 employees in the polyvinyl chloride and vinyl chloride operations. In the six known instances, there was an average of 20 years exposure per employee.

There is a great deal of testing going on at this time by a large number of organizations trying to determine the causes of the problem. One of the many chemicals being questioned, of course, is vinyl chloride; however, in the polyvinyl chloride operations where the incidents occurred, the workers were exposed to a larger number of other chemicals in the polyvinyl chloride process.

Our medical department has evaluated the work history and file of all the employees who were a part of the old Texas City VCM operations and find no evidence of any problems at Texas City.

We will continue to evaluate all of the material resulting from the studies being made and will keep you informed of any information pertinent to our particular situation.

We would like to re-emphasize. We find no problems at Texas City resulting from the old VCM operation.

TO BE USED ONLY IF OK'D BY ST. LOUIS

There is one series of blood tests that are being used to determine if there is any damage to the liver. These are called Liver Functions Tests and are normally used to determine liver damage from cases of Hepatitis. The tests do not tell you what caused damage to the liver, only that the liver isn't functioning properly.. We would be willing to offer these tests to the ex-VCM employees who desire to take them.

2/22/74

MONSANTO USED MATERIALS ON '76 NIOSH SUSPECT CARC. LIST*

8/4/76

NAME	CAS REG. NUMBER	NIOSH NO.	COMPANY**
Acrylonitrile	107131	AT 52500	1,2,3,6
Amaranth Extra	915673	QJ 65500	5,138
Aroclor 1254	11097691	CP 61250	5
Asbestos	1332214	CI 64750	4
Benzene	71432	CY 14000	3,4
Benzoyl Peroxide	94360	DM 85750	2,3,4,5
Benzyl Chloride	100447	XS 89260	3,5
Biphenyl	92524	DU 80500	3,4,5
Blue FD & C #1	2650182	BQ 45500	5 (138)
Blue FD & C #2	860220	DU 30000	5 (138)
Boric Acid	10043353	ED 45500	
Butasan	136232	ZH 01750	5
Cadmium	7440439	EU 98000	1
Cadmium Yellow	1306236	EV 31500	2
Calcium Chromate	10060089	GB 28000	
Carbon Tetrachloride	56235	FG 49000	
Chloroacetic Acid	79118	AF 85750	4,5
Chloroform	67663	FS 91000	5
C.I. - 12055	842079	QL 49000	2
C.I. - 16150	3761533	QJ 68250	2
C.I. - 77288	1308389		2,6
Cinnamyl Anthranilate	87296	CB 32000	5
Cobalt	7440484	CF 87500	3,5
Cobalt Oxide	1307966	GG 28000	3,5
Coumarin	91645	GN 42000	5
Cumyl Hydroperoxide	80159	MX 24500	3
Cyanuric Acid	108805	XZ 18000	5
Diallate	2303164	EZ 82250	4
2,4-Dichlorophenol	120832	SK 85750	5
Dicyclohexylamine	101837	HY 40250	5
Diethyl Sulfate	64675	WS 78750	1,3,4
Dimethoxane	828002	AH 13500	1
Ditertiary Butyl Peroxide	110054	ER 24500	2,3,4
Epichlorohydrin	106898	TX 49000	2,4
Epolene E	9002884	TZ 33250	1,2,4,6
Ethyl Alcohol	64175	KQ 63000	5,D
Ferrous Sulfate	7720787	NO 85000	3,4
Formaldehyde	50000	LP 89250	2,3,4,5
Gamma Butyrolactone	96480	LU 35000	4
Hexamethylene Tetramine	100970	MN 47250	2,4,5
Hydrazine	302012	MU 71750	3,4,5,7
Hydroquinone	123319	MX 35000	2,3,5
Indole	120729	NL 24500	5
Iso Amyl Alcohol	123513	EL 54250	5
Isobutyl Alcohol	78831	NQ 96250	2,3,4,5
Lactose	63423	OD 96250	5
Lauroyl Peroxide	105748	OF 26250	

(Cont'd.)

*List contains only materials indicated as showing carcinogen or neoplastic evidence.

	NAME	NUMBER	NIOSH NO.	COMPANY
	Maleic Anhydride	108316	CN 36750	2,3,5
	Mercury	7439976	OV 45500	3
	Methasan	137304	ZH 05250	5
	Methotrexate	59052	MA 12250	D
	Methyl Iodide	74884	PA 94500	3,5,7
	Methyl Methacrylate	80626	OZ 50750	2
H	Methylene Dianiline	101779	BY 54250	2
	N-Propyl Alcohol	71238	UH 82250	2,3
	Naphthalene	91203	QJ 05250	3,5
H	Nickel Carbonyl	13463393	QR 63000	4
H	Nickel Catalyst	7440020	QR 59500	1,3,4,5,7
	Nickel Oxide	1313991	QR 84000	5
	O-Chlorophenol	95578	SK 26250	3,5
	O-Toluidine	95534	XU 29750	5
	Oleic Acid	112801	RG 22750	1,2,5
	Ozone	10028156	RS 82250	
	P-Benzoquinone	106514	DK 26250	2
	P-Phenyl Phenol	92693	DV 58500	5
	Paracetaldehyde	123637	YK 05250	5
	Pentachlorophenol	87865	SM 63000	5
	Peracetic Acid	79210	SD 87500	3,5
	Petroleum Distillate	8002059	SE 71750	2
	Phenol	108952	SJ 33250	2,3
	Polyethylene Glycol	25322683	TQ 35000	2,3,4,5,6
	Polystyrene	9003536	WL 64750	2
	Polyvinyl Chloride	9002862	KV 03500	5
	Propylene oxide	75569	TZ 29750	3,5
	Safrol	94597	CY 28000	5
	Santocure MOR	102772	DL 59500	5
	Sodium Dichromate	10588019	HX 77000	
	Sodium Saccharin	128449	DE 45500	5
	Sorbic Acid	110441	WG 21000	5
	Styrene Oxide	96093	CZ 96250	2
	Tannic Acid	1401554	NW 50750	5
	Tertiary Butyl Perbenzoate	614459	SD 94500	2,7
	Tetraethyl Thiuram Disulfide	97778	JO 12250	5
	Thiotax	149304	DL 64750	5
	Thiourea	62566	XU 28000	2,5
H	Trichloroethylene	79016	KX 45500	1,4,5,6
	2,4,6-Trichlorophenol	88062	SN 15750	5
H	Vinyl Chloride	75014	KU 96250	2
	Violet FD & C #1	1694093	BQ 11400	5,(138)
	Yellow FD & C #6	2783940	QK 24500	5,(138)
	Zinc Chloride	7646857	ZH 14000	2,5
	Zinc Sulfate	7733020	ZH 52600	4,5

** 1 = MTC
2 = MPR
3 = MCI
4 = MAP
5 = MIC
6 = MCP
7 = MRC
138 = Fl. Essence

C.E.
Dec. '77

APPENDIX B

Toxic Effluent Standards - Sect. 307a FWPCA

Aldrin/dieldrin
DDT DDE DDD
Endrin
Toxaphene
Benzidine
PCB's

Hazardous Air Emission Standards - Sect. 112 CAA

Asbestos
Beryllium
Mercury
Vinyl chloride
Benzene (in development)
Acrylonitrile (intent announced)

12/2/77

2) Metabolic processes or mechanisms which counteract the effects of the chemical carcinogen after it reaches the target area,

3) Delays in development of cancer resulting in a latency period sufficiently long to insure intervention of an independent cause of death.

Some of the evidence for each of these types of threshold is summarized below.

It is now generally accepted that chemical carcinogenesis is initiated when electrophilic molecules (alkylating agents) are covalently bound to nucleophilic groups in certain cellular macromolecules (e.g., DNA and RNA). Moreover, most chemical carcinogens are not themselves chemically reactive but must be converted or "activated" by metabolic processes to form the necessary electrophilic species.[3/] Thus, if the physiological mechanisms invoked in absorption, distribution, metabolization, and excretion of small amounts of a carcinogenic substance can operate either to prevent metabolic activation or block access to reactive sites on vulnerable macromolecules, an exposure threshold exists for that carcinogen.[4/] The crucial

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3/ Heidelberger, C., Chemical Carcinogenesis, in Annual Review of Biochemistry, Volume 44, Eds. Snell, Boyer, Meister, and Richardson, at 79-121 (1975); Miller, J.A. and Miller, E.C., Chemical Carcinogenesis: Mechanisms and Approaches to Its Control, 47 J. Nat'l Cancer Inst. V-XIV (1971); Neumann, H. G., Ultimate electrophilic carcinogens and cellular nucleophilic reactants, 32 Arch. Toxicol. 27 (1974).

4/ Brown, C. C., Mathematical aspects of dose-response studies in carcinogenesis--The concept of threshold, 33 Oncology 62 (1976); Freese, E., Thresholds in toxic, teratogenic, mutagenic, and carcinogenic effects, Environmental Health Perspectives, December 1973, at 171.

parameter in cancer initiation is consequently not the ambient exposure, but the "effective dose" eventually delivered to the target area, which is likely to be "some complex function of the actual exposure along with the biochemical and physiological parameters of the host."[5/]

A metabolic threshold for chemical carcinogenesis could result whenever non-carcinogenic metabolic and excretary pathways are saturable and are supplanted by carcinogenic alternative pathways at higher dosages. As summarized below, several recent experiments have confirmed the existence of exactly this type of dose-dependent differential metabolism. Reviewing some of this recent evidence, P. J. Gehring and his colleagues concluded,

> Detoxification of many chemicals is a dose-dependent process which can be overwhelmed, leading to disproportionate increases in their toxicity, including carcinogenicity. When detoxification mechanisms are overwhelmed, there is a disproportionate retention of chemicals per se and/or their degradation products in the body, and reactions of reactive electrophilic metabolities of the chemicals with macromolecules are often enhanced greatly.[6/]

In some instances, a chemical may combine with other reactive substances[7/] or be rapidly excreted before it can be

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5/ Brown, C. C., note 4 supra, at 63.

6/ Gehring, P. J., Watanabe, P. G., Young, J. D., and Le Beau, J.E., Metabolic thresholds in assessing carcinogenic hazard, Toxicology 56 (1976), at 56.

7/ Kolbye, C., Jr., Cancer in humans: Exposure and responses in a real world, 33 Oncology 90 (1976), at 94.

converted to an electrophilic metabolite. For example, furosemide is excreted primarily via the kidney at low dosages. However, at higher dosages, renal elimination is overwhelmed and the formation of toxic metabolites which react with macromolecules increases disproportionately.[8/]

Once electrophilic metabolites have been formed, they can be detoxified before reacting with macromolecules by various saturable enzymatic and non-enzymatic pathways, including conjugation with glutathione, sulfate, or glucuronide.[9/] For example, bromobenzene is detoxified by conversion to the glutathione conjugate. However, when glutathione stores are depleted by higher bromobenzene dosages, alkylation of macromolecules by the reactive electrophilic metabolite increases dramatically.[10/]

Recent studies of the metabolization in rats of vinyl chloride monomer (VCM), a known human carcinogen, confirm that low doses of VCM are detoxified by conjugation with nonprotein sulfhydryl groups in glutathione. However, administration of higher doses results in depletion of

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8/ Gillette, J.R., A perspective on the role of chemically reactive metabolites of foreign compounds in toxicity--I. Correlation of changes in covalent binding of reactivity metabolites with changes in the incidence and severity of toxicity, 23 Biochem. Pharm. 2785 (1974), and II. Alterations in the kinetics of covalent binding, 23 Biochem. Pharm. 2927 (1974).

9/ Gehring, et al., note 6 supra.

10/ Gillette, note 8 supra.

hepatic nonprotein sulfhydryl content, freeing the electrophilic metabolites of VCM to react with cellular macromolecules such as DNA and RNA.[11] These studies indicate that "there is a threshold of exposure in rats at which the ability to replace sulfhydryl groups is not overwhelmed and physiologic defense mechanisms remain fully operative."[12] According to H. E. Stockinger, these findings "must be accepted as indisputable biological evidence for a threshold for vinyl chloride carcinogenesis in rats."[13]

The identification of similar thresholds for other chemical carcinogens, also derivative of dose-dependent variation in metabolism, is likely and may "prove to be the rule rather than the exception."[14] In fact, the eminent cancer researchers Miller and Miller have observed,

> [I]nhibition of carcinogenesis via trapping of the ultimate carcinogen(s) with noncritical nucleophiles probably occurs to some extent with all chemical carcinogens and may provide a natural protective mechanism . . . . The removal of ultimate carcinogenic forms through noncarcinogenic reactions may be an important factor in the determination of threshold doses of carcinogens . . . .[15]

11/ Hefner, R.E., Jr., Watanabe, P.G., and Gehring, P.J., Preliminary studies of the fate of inhaled vinyl chloride monomer in rats, 246 Ann. N.Y. Acad. Sci. 135 (1975); Watanabe, P.G., Hefner, R.E., Jr., and Gehring, P.J., Vinyl chloride incuded depression of hepatic non-protein sulfhydryl content and effects on bromsulfalein clearance in rats, 6 Toxicology 1 (1976), Gehring, et al., note 6 supra.

12/ Gehring; et al., note 6 supra, at 69.

13/ Stockinger, H.E., Presentation before the National Drinking Water Advisory Council, August 25, 1976, at 6.

14/ Gehring, et al., note 6 supra, at 70.

15/ Miller and Miller, note 3 supra, at XII.

Dose-dependent variation in metabolism is not the only argument for the existence of thresholds for chemical carcinogenesis. Several reputable authorities have argued that cancer induction should not be expected unless the number of carcinogen molecules in a given target cell exceeds a stochastic threshold.[16/] According to these theorists, any substance must be present in a minimum number of molecules or particles in order to exert a deleterious effect on the host organism.

It is appropriate to note that some of the most often cited evidence for the notion that there is no threshold for chemical carcinogenesis is derived from studies of radiation induced cancer which suggest a linear dose-response relationship. However, only the briefest consideration is necessary to conclude that such evidence is basically inapposite to the problem of chemical carcinogenesis. While a chemical carcinogen may be metabolically deactivated or

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16/ Claus, G., Environmental carcinogens: Is there a threshold of exposure? 7 Clin. Toxicology 497 (1974); Claus, G., Krisko, G., and Bolander, K., Chemical carcinogens in the environment and in the human diet: Can a threshold be established? 12 Food Cosmet Toxicology 737 (1974); Dinman, B.D., "Non-concept" of "no-threshold": Chemicals in the environment - Stochastic determinants impose a lower limit on the dose-response relationship between cells and chemicals, 125 Science 405 (1972); Stockinger, H.E., Concepts of thresholds in standards setting, 25 Arch. Env. Health 153 (1972).

encounter physiological barriers such as impermeable membranes before it achieves the necessary proximity to crucial macromolecules, the likelihood that a particle of radiation will penetrate and damage the nucleus of a given cell is determined only by the mass of the intervening tissue.[17/] In any event, "it is not yet feasible to define the kinetics . . . or to prove the existence or absence of a threshold dose" for radiation carcinogenesis.[18/]

Even if metabolic mechanisms are not sufficient to prevent the carcinogen or its metabolites from reacting with critical receptor sites, other metabolic mechanisms may still be sufficient at low doses to prevent induction of cancer. In particular, DNA repair mechanisms can prevent point mutations caused by alkylation of DNA from resulting in permanent genetic alterations, and immunological surveillance can prevent proliferation of cancerous cells.

Though a number of different types of DNA repair appear to be operable in mammalian tissue,[19/] "dark repair" or

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17/ Kolbye, C., Jr., note 7 supra, at 96; Gehring, P. J. and Blau, G. E., Mechanisms of carcinogenesis: Dose reponse, Presented at the Environmental Carcinogenesis Conference in Houston, Texas, January 12-13, 1977, ____ Toxicol. Appl. Pharmacol. ____, at 9-10.

18/ Upton, A.C., The dose-response relation in radiation-induced cancer, 21 Cancer Research 717 (1961), at 726.

19/ Trosko, J.E. and Chu, H.Y., The role of DNA repair and somatic mutation in carcinogenesis, 21 Adv. Cancer Research 391 (1975).

"unscheduled DNA synthesis," which involves excision of damaged DNA segments by special enzyme systems, is thought to be of greatest importance in man.[20] Recent research has demonstrated a clear correlation between the capability of various tissues to enzymatically excise alkylated lesions and the susceptibility of such tissues to carcinogenesis.[21] The existence of DNA repair mechanisms is of great significance to the threshold issue because they "may be able to handle only a limited number of DNA alterations and be overwhelmed by too high concentrations of a mutagen,"[22] resulting in an exposure threshold.

There is considerable evidence that immunological surveillance against clones of malignant cells is very important in prevention of cancer. For example, the incidence of cancer in kidney transplant patients who have taken immunosuppressive drugs is eighty times higher than in the general population.[23]

20/ Mitchell, A.D., The potential utility of DNA repair for predicting the effects of human exposure to hazardous agents, Presented at the NIEHS Conference on the Problems of Extrapolating the Results of Laboratory Animal Data to Man and of Extrapolating the Results from High Dose Level Experiments to Low Dose Exposures, in Pinehurst, North Carolina, March 10-12, 1976.

21/ Kleihues, P. and Cooper, H.K., Repair excision of alkylated bases from DNA in vivo, 33 Oncology 86 (1976).

22/ Freese, note 4 supra, at 174.

23/ Penn, A., Starzl, T.E., 14 Transplantation 407 (1972).

Since many chemical carcinogens have been shown to induce immunological depression in laboratory animals,[24] it is likely that immunological surveillance is substantially more effective at low exposure levels, indicating a possible exposure threshold.

One particularly persuasive and lucid argument for exposure thresholds for chemical carcinogenesis is provided by recent research which demonstrates the existence of a quantitative inverse relationship between dosage of a carcinogen and the latency period for cancer development, i.e., as a dosage is decreased, the latency period is increased. This relationship was first identified by H. Druckery of West Germany, who used the results of an ingenious series of experiments relating dose and latency period to derive the formula

$$dt^n = k$$

where d equals dosage, t equals time elapsed to tumor appearance, n is a number between two and four, usually about three, and k is a constant.[25] In another more recent study,

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24/ Laroye, G.J., How efficient is immunological surveillance against cancer and why does it fail? 1 Lancet 1097 (1974).

25/ Druckrey, H., Quantitative aspects in chemical carcinogenesis, in Potential Carcinogenic Hazards for Drugs-Evaluation of Risks, Ed. R. Truhaut, UICC Monograph Series, vol. 7, Springer-Verlag (1967), at 60-78.

Jones and Grendon used both laboratory and epidemiological data to derive essentially the same formula, and proposed a corresponding hypothesis regarding the mechanism of cancer induction.[26]

The inverse relationship between dosage and latency period necessarily implies the existence of a real exposure threshold, in that at sufficiently low exposure levels the time required for tumor development will exceed the expected lifespan of the exposed population. Moreover, since the Druckrey formula has been found to be consistent with data from many different epidemiological and laboratory studies, it should be of considerable utility in calculating actual exposure thresholds.[27] When the inverse relationship between dosage and latency period is considered in combination with the evidence for various metabolic thresholds, the case for an exposure threshold for chemical carcinogenesis is compelling indeed.

II. Many Apparent Carcinogens are in Fact Cocarcinogens or Secondary Carcinogens Which Affect the Incidence of Cancer Only When the Cumulative Dose is Sufficient to Disturb Metabolic Equilibria.

26/ Jones, H.B. and Grendon, A., Environmental factors in the origin of cancer and estimation of the possible hazard to man, 13 Food Cosmet. Toxicol. 251 (1975).

27/ See, e.g., Albert, R.E. and Altshuler, B., Considerations relating to the formulation of limits of unavoidable population exposures to environmental carcinogens, in Radionuclide Carcinogenesis, Proceedings of the Twelfth Annual Hanford Biology Symposium at Richland, Washington, May 10-12, 1972, Atomic Energy Commission Office of Information Services (1973), at 234-253; Salsburg D.S., Mantel-Bryan - Its faults and alternatives available after thirteen more years of experimentation, 30 Food, Drug and Cosmetic L.J. 116 (1975).

Because a variety of chemical carcinogens commonly occur both in the food supply and in the environment, evidence of a correlation between exposure to a given substance and increased incidence of cancer is often insufficient to establish the actual role of the substance in cancer induction. Indeed, the National Cancer Advisory Board recently observed, "[I]n most of the current human epidemiologic approaches and certain animal bioassays it is not possible to differentiate clearly between initiating agents, promoting agents, and certain modifying factors."[28/] This observation is crucial, because the existence of thresholds for promoting agents and modifying factors is not questioned.

Chemicals which facilitate expression of the carcinogenic potential of an independent agent or agents are referred to variously as cocarcinogens or secondary carcinogens. They may operate either by increasing the susceptibility of given cells to malignant transformation or by facilitating metabolic activation of a primary carcinogen.[29/] The distinction between

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28/ National Cancer Advisory Board, General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances: Report of the Subcommittee on Environmental Carcinogenesis, 58 J. National Cancer Inst. 461 (1977)

29/ See, generally, Bingham, E. and Falk, H.L., Environmental carcinogens - The modifying effect of cocarcinogens on the threshold response, 19 Arch. Env. Health 779 (1969); Falk, H.L., Possible mechanisms of combination effects in chemical carcinogenesis, 33 Oncology 77 (1976); Kolbye, note 7 supra.

cocarcinogens and secondary carcinogens is somewhat vague. It would appear that a chemical is usually referred to as a cocarcinogen when it has been observed to potentiate the effects of specific chemical initiating agents and as a secondary carcinogen when the postulated mechanism involves a more general metabolic disturbance or toxic insult. In any event, there is general agreement that these substances must be present in substantial amounts in order to facilitate induction of cancer.30/

A. C. Kolbye, an Associate Director of FDA, observed in a recent article:

> Many so-called "carcinogens" are poorly defined as to their toxicological effects which in some instances may decrease resistance to an independently caused cancer. Some "carcinogens" are probably not carcinogenic per se, but through their toxicity effects can decrease resistance to other causative factors present in control animals or in their environment or diet. The detection of a positive carcinogenic result should serve as a warning that a critical convergence of events can take place resulting in an increased incidence of cancer . . . .
>
> The expression of toxicity is generally a dose-related phenomenon that behaves much as do pharmacologically active agents in that there are relatively clear gradations of qualitative response of cells, tissues, or organs to different levels of toxic insult . . . . When a threshold is crossed, the cell, tissue, organ, or organism incurs a functional shift in physiological per-

30/ Falk, note 29 supra; Kolbye, note 7 supra; Weisburger, J.H., Environmental cancer, 18 J. Occupational Medicine 245 (1976); World Health Organization, Assessment of the Carcinogenicity and Mutagenicity of Chemicals, Technical Report No. 546 (1974).

> formance in response to a cumulated dose . . . . If certain functional capabilities are important to maintaining normality in a cell, or serve to protect against induction of malignant changes, then alterations of these functions are likely to be important factors in the critical convergence of events that precede the induction of cancer.[31]

Thus, whenever a chemical "carcinogen" actually operates by inducing functional changes or disturbing metabolic equilibria, the chemical in question will be "carcinogenic" only above a given exposure threshold.

It is not surprising that chemical exposures sufficient to cause a toxic or pathological response sometimes cause cancer. Cancers often develop in chronically inflamed or scarred tissue.[32] Subcutaneous injections of such common substances as water and glucose have been observed to cause cancer, presumably as a result of local irritation.[33]

Recent studies of 1, 4-dioxane, a chemical which induces hepatomas and nasal carcinomas in rats, indicate that it is carcinogenic only when administered at doses sufficient to cause death and severe pathology of the liver and kidney. Intermediate dosages, which are still sufficient to cause morphological damage of liver and kidney tissues, are apparently not carcino-

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[31] Kolbye, note 7 supra, at 94, 96.

[32] Laroye, note 24 supra, at 1098.

[33] Grasso, P. and Golberg, L., Subcutaneous sarcoma as an index of carcinogenic potency, 4 Food Cosmet. Toxicol. 297 (1966).

genic.[34/] On the basis of this evidence, it appears likely that 1, 4-dioxane is a secondary carcinogen and induces cancer only when exposure levels exceed a threshold of toxicity.

Administration of Myrj 45 (polyoxyethylene monostearate) in rats provides another example of secondary carcinogenesis. Resulting cancers of the urinary bladder are thought to result from the presence of bladder calculi induced by the chemical rather than from its direct action.[35/]

It is often difficult to demonstrate conclusively that a given chemical carcinogen induces cancer directly rather than by disturbing metabolic equilibria. Carcinogens which operate by facilitating the expression of other causative factors are likely to be inactive below a critical exposure threshold. Consequently, attempts should be made to identify the mechanism of carcinogenesis for each individual carcinogen as precisely as possible before setting regulatory standards based on the hypothetical effects of low exposures.

34/ Kociba, R.J., McCollister, G.B., Park, C., Torkelson, J.R., and Gehring, P.J., 1, 4-Dioxane. 1. Results of a two-year ingestion study in rats, 30 Toxicol. Appl. Pharm. 275 (1974); Argus, M. T., Sohal, R.S., Bryant, G.M., Hoch-Ligeti, C., and Arcos, J.C., Dose-response and ultrastructural alterations in dioxane carcinogenesis, 9 Eur. J. Cancer 237 (1973).

35/ World Health Organization, note 30 supra, at 11.

III. Even if Variability in Individual Susceptibility to a Given Chemical Precludes Identification of an Absolute Threshold for Carcinogenicity, There is a "Practical" Threshold Which Represents an Infinitesimal Risk to the Exposed Population.

As summarized above, the evidence for existence of threshold effects in chemical carcinogenesis is considerable. However, demonstration that a particular carcinogen exhibits threshold behavior may not enable determination of a single exposure threshold which is applicable to every individual in the exposed population. This potential lack of uniformity is a consequence of genetic variability in some of the parameters most likely to contribute to threshold phenomena, such as microsomal enzyme inducibility,[36/] DNA repair capability,[37/] and immunological competence.[38/]

Variability in individual susceptibility should not diminish the significance of threshold evidence to the enlightened policy maker. On the contrary, identification of hypersusceptible individuals with genetically

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36/ Kellerman, G., Shaw, C.R., Luyten-Kellerman, M., Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma, 289 N. Engl. J. Med. 934 (1973).

37/ Robbins, J.H., Kraemer, K.H., and Lutzner, M.A., Xeroderma pigmentosum. An inherited disease with sun sensitivity, multiple cutaneous neoplasma, and abnormal DNA repair, 80 Ann. Intern. Med. 221 (1974).

38/ Laroye, note 24 supra.

lower thresholds could be a very important component of cancer prevention policy.[39] However, if hereditary variation in thresholds is significant, this suggests that the analyst should be interested in identification of a "practical" threshold which represents an acceptable risk to the exposed population.

The most well known method for estimation of a "practical" threshold is the procedure introduced by Mantel and Bryan, who recommended use of linear regression, with an arbitrarily assigned slope of one probit per tenfold increase in dose, to extrapolate from observed dose-response data to the dose corresponding to a hypothetical cancer risk of one in 100,000,000.[40] This procedure has considerable advantages in that it is relatively straitforward and easily applicable to a wide variety of experimental data. However, extrapolation methodologies based on statistical functions have no real basis in any hypothesis as to the mechanism of

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39/ See Stockinger, H.E., Pharmacogenetics in the detection of the hypersusceptible worker, 151 Ann. N.Y. Acad. Sci. 968 (1968); Stockinger, note 16 supra, at 157; Stockinger, note 13 supra, at 9-10.

40/ Mantel, N. and Bryan, M.R., "Safety" testing of carcinogenic agents, 27 J. Nat. Cancer Inst. 455 (1961); Mantel, N. Bohidar, N.R., Brown, C.C., Ciminera, J.L., and Tukey, J.W., An improved Mantel-Bryan procedure for "safety" testing of carcinogens, 35 Cancer Research 865 (1975); Mantel, N. and Schneiderman, M.A., Estimating "safe" levels, a hazardous undertaking, 35 Cancer Research 1379 (1975).

cancer induction.[41] Moreover, they fail to incorporate the reductions in toxic stress and changes in metabolic and excretory pathways which can be associated with decreasing dosage.[42] Consequently, they are little more than convenient fictions.

The completely arbitrary nature of statistical extrapolation techniques when applied to prediction of dose-response relationships at low dosages can best be illustrated by an example. Though several different statistical dose-response functions (the probit, logit, and one-particle curves) are all very similar within the observable range, the predicted practical threshold or "virtually" safe dose of Mantel and Bryan varies from one-hundredth to one-one-millionth of the TD1 (the dose which causes a maximum tumor incidence of one per cent), depending on which statistical function is selected.[43] Little wonder that the Panel on Carcinogenesis of the FDA Advisory Committee on Protocols for Safety Evaluation

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41/ Hoel, D.G., Statistical extrapolation methods for estimating risks from animal data, 271 Ann. N.Y. Acad. Sci. 418 (1976); Salsbury, note 27 supra, at 116-8; Weil, C.S., Statistics vs. safety factors and scientific judgment in the evaluation of safety for man, 21 Toxicol. Appl. Pharm. 454 (1972).

42/ Gehring and Blau, note 17 supra.

43/ FDA Advisory Committee on Protocols for Safety Evaluation, Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides, 20 Toxicol. Appl. Pharm. 418 (1971), at 430-3.

concluded, "[I]t would be imprudent to place excessive reliance on mathematical sleight of hand, particularly when the dose-response curves used are largely empirical descriptions, lacking any theoretical physical or chemical basis."[44/]

An additional problem with statistical extrapolation methodologies is that they entail an a priori assumption that the viability of physiological defense mechanisms and the metabolic fate of the carcinogen are not dose dependent. Mantel has acknowledged that the Mantel-Bryan Procedure is "essentially a conservative one."[45/] In a recent study, Gehring and Blau utilized dose-dependent or nonlinear pharmacokinetics to demonstrate that statistical extrapolation techniques are likely to substantially overestimate risk at low dosages.[46/] Consequently, setting exposure standards on the basis of statistical extrapolations can be "highly misleading, resulting in unnecessarily conservative 'permissible exposures'. . . ."[47/]

44/ Id. at 433.

45/ Mantel, N., Conservation and "safe" dose estimates by the Mantel-Bryan procedure.

46/ Gehring and Blau, note 17 supra.

47/ Claus, et al., note 16 supra, at 745.

The chief defects of all statistical extrapolation methodologies are: (1) they have no theoretical basis, and (2) they involve a false a priori assumption that the proportion of the carcinogen actually delivered in an activated form to the target area (the "effective dose") is not-dose-dependent. Consequently, calculations of "practical" exposure thresholds which represent an acceptable quantum of risk are more likely to be meaningful and realistic if they are based on plausible stochastic models of carcinogenesis such as those proposed by Armitage and Doll[48/] and Neyman and Scott[49/] and non-linear pharmacokinetic models such as that proposed by Gehring and Blau.[50/]

48/ Armitage, P. and Doll, R., Stochastic models for carcinogenesis, in Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability, vol. IV, Ed. Neyman, J. Univ. Cal. Press (1961), at 19-38.

49/ Neyman, J. and Scott, E. L., Statistical aspects of the problem of carcinogenesis, in Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability, vol. IV, Ed. LeCam, L.M. and Neyman, J., Univ. Cal. Press (1967), at 745-776; see also Salsbury, note 27 supra, at 120-1.

50/ Gehring and Blau, note 17 supra.